VALUE IN HEALTH 14 (2011) 937–943

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Patient Preference for Latent Tuberculosis Infection Preventive Treatment: A Discrete Choice Experiment

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ABSTRACT

Objectives: To quantify patient preferences when making decisions as to whether to accept latent tuberculosis infection (LTBI) preventive treatment, using a discrete choice experiment (DCE). **Methods:** A DCE survey was developed and administered to LTBI patients. Each patient was given 10 random choices along with two fixed choices to check consistency. Two hypothetical treatment options and one opt-out option were presented in each choice task. Latent class analysis was conducted to estimate preferences for six key treatment attributes. **Results:** Among the 214 respondents, 194 (90.7%) who provided valid DCE responses and complete sociodemographic information were included. Results consistently suggested that respondents were averse to higher risk of active tuberculosis and side effects and longer treatment. A three-latent-class model with five covariates was chosen. Forty-seven percent of the respondents were assigned to class 1, 32% to class 2, and 21% to class 3. Although all six attributes were shown to significantly influence the respondents' treatment decision, the risk of active tuberculosis, chance of liver damage, and frequency of clinic visits were the most important ones. Significant preference heterogeneity was observed in two attributes: frequency of clinic visits ($P < 0.01$) and chance of liver damage developing ($P < 0.01$). Class 1 individuals were most likely to have children. Class 2 had the highest employment rate. Class 3 respondents tended to choose the opt-out option on DCE tasks and were more likely to be born outside Canada, have higher education, and be unemployed. **Conclusion:** Respondents consistently preferred preventive treatment with higher effectiveness, fewer side effects, and shorter length. Substantial preference heterogeneity existed among respondents.

Keywords: discrete choice experiment, latent class analysis, stated preference, tuberculosis.

Introduction

Tuberculosis (TB) continues to be a major public health threat with one-third of world's population infected [1,2]. Among immunocompetent individuals with latent TB infection (LTBI), in approximately 10%, it will progress to active TB disease during their lifetime. Because the majority of new active TB cases arise in people with LTBI, preventing LTBI from developing into clinical disease has both individual benefits and public health significance [3,4]. Isoniazid (INH) has been long used for preventive treatment and has well-established efficacy as demonstrated by the results of multiple clinical trials [5–7]. The effectiveness of preventive treatment in practice, however, has been limited by low acceptance and poor adherence among patients [8–11]. In British Columbia (BC), individuals with a diagnosis of LTBI are encouraged to see a physician to discuss preventive treatment, which consists of 9 months of INH managed through the TB clinics at the BC Centre for Disease Control (BCCDC). The treatment is publicly funded and is optional for the patients. In 2004, in BC, 49.2% of people offered preventive treatment agreed to initiate it; approximately 50% of these eventually completed it [4].

A large body of research has intended to identify sociodemographic factors and other modifiable predictors associated with poor adherence among patients receiving LTBI treatment [8–11]. However, patients' treatment decision -making has only been investigated rarely [12]. Treatment decision making is a complex behavior, depending not only on the probability of risks and benefits, but also on how patients perceive and value these parameters and the associated uncertainties. As such, more effort needs to be taken to understand the preferences influencing the acceptance of LTBI treatment. The primary objective of this study was to understand patients' treatment decision-making processes through quantifying their preferences for the preventive treatment using a preference-elicitation technique: a discrete choice experiment (DCE).

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1098-3015/$36.00 – see front matter Copyright © 2011, International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Published by Elsevier Inc.
doi:10.1016/j.jval.2011.05.003

Originating from marketing, transport economics, and environmental economics, DCE methods have been recently adopted in the health-care sector for a wide range of applications, e.g., understanding the decision-making process of patients and health-care professionals, estimating willingness to pay, and predicting immunization uptake rates [13,14]. Based on Lancaster's economic theory of value, DCE assumes the commodity or product of interest can be described by a few of its attributes or characteristics, individuals derive utility from these underlying attributes rather than the commodity per se, and individuals have preference or utility for these attributes, which can be estimated through the choices that they make [13,14].

To quantify respondents' preferences, choices made in a DCE survey are analyzed under a random utility theory framework [13]. Traditional logit or probit modeling approaches to analyzing choice data are limited because they assume homogeneity of preferences among respondents. Preferences for some treatment and procedure attributes are expected to vary considerably across individuals, which may be related to observed factors (e.g., treatment attributes and respondents' sociodemographic features) and unobservable characteristics (e.g. respondents' attitude and personality) [15–17]. Ignoring the heterogeneity may bias the preference estimates and lose the richness of information that could be uncovered [16].

Mixed logit and latent class analysis are common approaches to deal with preference heterogeneity and estimate the distribution of preferences for the attributes. In addition, latent class modeling facilitates the grouping of respondents into a finite number of latent classes with distinct preferences. The probability of class membership and class-specific preference parameters can be estimated. Often used in marketing research, latent class analysis could produce results leading to effective product targeting and strategic positioning.

Methods

Development of the DCE survey

To identify treatment attributes for the DCE survey, semistructured individual interviews were conducted at the BCCDC TB clinic. Twenty newly diagnosed LTBI patients were purposively recruited to ensure that half of them had accepted the treatment and half had declined it. After discussing with the physician, the patients were invited to talk about their perceived motivating factors and barriers of initiating the preventive treatment. Based on interview results and expert opinions, six key attributes with various levels (Table 1) were chosen: 1) length of treatment; 2) frequency of clinic visits; 3) risk of the development of active TB disease after treatment, which was used as an indicator of the treatment effectiveness; 4) chance of liver damage developing; 5) chance of skin rash developing; and 6) chance of fatigue developing.

Sawtooth CBC/SSI Web V6.4.2 (Sawtooth Software, Inc., Sequim, WA) was used to generate 12 versions of DCE questionnaires. A fractional factorial experiment design was applied where orthogonality, level balance, and minimal overlap were taken into account [18]. Each version had 10 random choice sets plus two identical fixed choices, and an example choice set is presented in Figure 1. In each choice set, respondents were asked to compare two hypothetical treatment options (A and B) and choose their preferred one. An opt-out option of "neither" was also available [19], which was explicitly defined as "lifetime risk of 10% of developing active TB disease without taking preventive treatment and no risk of side effects."

Located at question numbers 1 and 11 in the survey, the fixed choices were included to check the validity and internal consistency of the DCE design and responses [20,21]. In the fixed choice set, one treatment option had clearly dominant or better attribute levels, i.e., shorter but more effective and having fewer side effects. Respondents were expected to choose the better treatment option if they understood the task and made rational decisions. Responses to fixed choice sets were not included in data analysis. In random choice tasks, on the other hand, treatment options were carefully checked to limit the number of dominant scenarios where no trade-off was needed. The survey was pilot tested among 60 LTBI patients before final administration.

Table 1 – Attributes and levels to describe latent tuberculosis infection preventive treatment.

Treatment attribute	Levels	Neither option
Length of treatment	4, 6, 9, and 12 mo	None
Frequency of clinic visit	Every 2 mo, every 1 mo, every 2 wk	None
Risk of active TB developing after treatment	0%, 1%, 2%, 4%	10%
Chance of liver damage developing	0%, 1%, 3%, 5%, 10%	0%
Chance of skin rash developing	0%, 5%, 10%	0%
Chance of fatigue developing	0%, 5%, 10%	0%

TB, tuberculosis.

Subject recruitment and data collection

Subjects were recruited through BCCDC TB clinics if they 1) had a diagnosis of LTBI, 2) were 19 years or older, and 3) were able to read and understand English. Ethics approval was obtained from the University of British Columbia Behavioural Research Ethics Board. Data were collected using a questionnaire that included the DCE survey and sociodemographic and TB-relevant information, such as the reason for having a tuberculin skin test (TST) and bacille Calmette-Guérin (BCG) vaccination status. A warm-up DCE choice set was completed by each respondent. The subject could complete the questionnaire at the clinic or complete it elsewhere and bring it back on the next clinic visit.

Statistical analysis

Respondents were defined as consistent if they chose the better treatment alternative or the neither option in the fixed consistency-check choice sets. Respondents who were inconsistent on both fixed questions or had incomplete sociodemographic information were excluded from data analysis. The sociodemographic characteristics of included respondents were summarized using descriptive statistics.

DCE choice data were analyzed using latent class analysis to account for the preference heterogeneity among respondents. All attribute variables were evaluated on a continuous scale except for the variable frequency of clinic visits, which was effect coded [22].

To determine the optimal number of latent classes, we estimated a series of models with an increasing number of classes from 2 to 10. Three information criteria, including log-likelihood, Akaike Information Criteria, and Bayesian Information Criteria, were used as a statistical guide to how many classes to retain, i.e., the optimal number of classes was determined when an additional class would not significantly improve the model fit [15–17]. The significance of parameter estimates and the practical interpretability of class membership were also considered. A manual backward selection method was used to investigate sociodemographic and other relevant variables for inclusion in the final la-

Treatment Features	Treatment A	Treatment B	Neither
Length of treatment	**12 months** of 1 pill daily	**9 months** of 1 pill daily	No Treatment
Frequency of clinic visit	**Every 2 weeks**	**Every 2 months**	None
Risk of developing active TB after treatment (benefit)	**0 out of 100 (0%)**	**4 out of 100 (4%)**	**10 out of 100 (10%)**
Chance of developing liver damage (side effect)	**1 out of 100 (1%)**	**5 out of 100 (5%)**	0 out of 100 (0%)
Chance of developing skin rash (side effect)	**0 out of 100 (0%)**	**10 out of 100 (10%)**	0 out of 100 (0%)
Chance of developing fatigue (side effect)	**5 out of 100 (5%)**	**0 out of 100 (0%)**	0 out of 100 (0%)
Which would you choose? **(tick only one box)**	Prefer Treatment A ☐	Prefer Treatment B ☐	Prefer No Treatment ☐

Fig. 1 – Example of a discrete choice experiment choice set.

tent class model as covariates, based on their influences on the class membership.

Latent class analysis was performed using Latent GOLD version 4.5 (Statistical Innovations Inc., Belmont, MA) and other analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC).

Results

Respondents characteristics

Among the 214 respondents (Fig. 2), 10 (4.7%) were inconsistent on both fixed choice sets and were excluded from data analysis; 4 (1.9%) chose the neither option throughout the survey irrespective of the attribute levels given (i.e., nondemanders). Therefore, a total of 204 (95.3%) were consistent on at least one fixed question. After further excluding 10 respondents with incomplete sociodemographic information, 194 (90.7%) were included in choice data analysis.

Table 2 summarizes the baseline characteristics of the 194 respondents. Their average age was 38.0 years and 61.9% were female. Of the respondents, 85.6% were born outside Canada and 68.6% had Asian background. Among the 194 respondents, 80.9% had college/university or higher education and 64.9% were currently employed. Of the respondents, 22.2% reported having other health conditions, e.g., hypertension, arthritis, and diabetes. The reasons for doing a screening TST varied: 19.6% were exposed to an active TB patient, 16.5% did it for a medical reason or doctor's

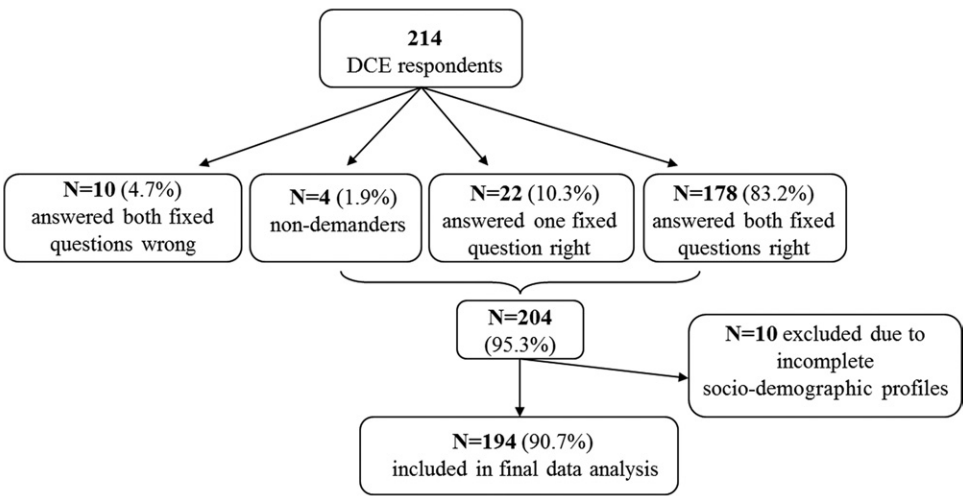

Fig. 2 – Respondent recruitment and inclusion.

Table 2 – Description of respondent baseline characteristics.

Baseline characteristics	N = 194
Mean age, y (SD)	38.0 (11.8)
Female, n (%)	120 (61.9)
Born outside Canada, n (%)	166 (85.6)
Ethnic origin, n (%)	
Asian	133 (68.6)
White	50 (25.8)
Others	11 (5.7)
Marital status, n (%)	
Single	74 (38.1)
Married	102 (52.6)
Others	18 (9.3)
Have children, n (%)	104 (53.6)
Education, n (%)	
High school or less	37 (19.1)
College/university	123 (63.4)
Postgraduate	34 (17.5)
Employed, n (%)	126 (64.9)
Annual household income*, n (%)	
0–19,999	48 (24.7)
20,000–39,999	52 (26.8)
40,000–59,999	33 (17.0)
60,000–99,999	23 (11.9)
≥100,000	26 (13.4)
Prefer not to answer	12 (6.2)
Comorbidity, n (%)	43 (22.2)
On prescription medications, n (%)	69 (35.6)
On OTC medications, n (%)	32 (16.5)
BCG vaccination status, n (%)	
Yes	100 (51.5)
No	37 (19.1)
Not sure	57 (29.4)
Reason for TST, n (%)	
Contact of active TB case	38 (19.6)
Medical reason/Dr. referrals	32 (16.5)
School/employment/immigration	124 (63.9)
Know someone who had active TB, n (%)	51 (26.3)

* In Canadian dollars. BCG, bacille Calmette-Guérin; OTC, over the counter; TB, tuberculosis; TST, tuberculin skin test.

recommendation, and 63.9% for school, employment, or immigration screening. Half of the respondents believed that they had received BCG vaccination in the past.

Preference for LTBI treatment

Although the three model-fit statistical indicators did not show clear convergence on an optimal number of latent classes, their values were all leveling off at three- or four-class models and additional increase in model fit with increasing number of classes was marginal. Overall, including sociodemographic covariates further improved the model fit. After further consideration of the model simplicity and the interpretability of class membership, a three-class model with five sociodemographic covariates was chosen.

The class probabilities indicated that 47% of respondents were assigned to class 1, 32% to class 2, and 21% to class 3. Table 3 presents the class-specific preference estimates, and the relative importance of the six treatment attributes to each class is shown in Figure 3.

As seen in Table 3, the preference estimates had the expected direction. Respondents were consistently averse to a longer treatment regimen and higher risk of active TB, liver damage, skin rash, and fatigue. Respondents were more concerned about serious treatment side effects (i.e., liver damage) compared to relatively mild ones (i.e., skin rash and fatigue). Among the six attributes, chance of skin rash, chance of fatigue, and length of treatment were of least importance to most respondents. These findings were generally plausible and in line with our expectations, which supported the theoretical validity (often assessed by determining whether the estimated coefficients are of the anticipated signs and consistent with a priori expectation) of our DCE methodology.

There was substantial heterogeneity in preferences across the three classes, as indicated by differences in the sign, magnitude, and significance of the class-specific parameter estimates (Table 3). The Wald statistic (Table 3) tests the statistical difference of the preference estimates across the three classes and suggested that significant preference heterogeneity among the three classes existed in two attributes, frequency of clinic visits ($P < 0.01$) and chance of liver damage developing ($P < 0.01$).

Class 1 respondents had the lowest probability of choosing the neither option in the DCE survey. They considered risk of active TB developing and frequency of clinic visits most important (Fig. 3) when choosing treatment, and they preferred a clinic visit every 1 month over the other frequency options. Monthly clinic visits are the current practice at BCCDC TB clinics. Individuals in class 2 were most averse to the chance of liver damage developing (Fig. 3). They preferred clinic visits every 2 months over other options. Class 3 respondents had the highest probability of choosing the neither option in the DCE survey. In class 3, respondents placed similarly important values on the risk of active TB developing, chance of liver damage developing,

Table 3 – Class-specific preference estimates.

Treatment attribute	Class 1 mean (SE)	Class 2 mean (SE)	Class 3 mean (SE)	Wald P value
Length of treatment	−0.08 (0.02)*	−0.01 (0.03)	−0.09 (0.04)*	0.17
Frequency of clinic visit				<0.01†
No visit	−2.29 (0.45)*	−1.73 (0.44)*	1.80 (0.54)*	
Every 2 mo	0.67 (0.18)*	0.69 (0.19)*	−0.60 (0.24)*	
Every 1 m	0.99 (0.17)*	0.65 (0.20)*	−0.55 (0.24)*	
Every 2 wk	0.63 (0.16)*	0.39 (0.16)*	−0.65 (0.23)*	
Risk of active TB developing	−0.33 (0.04)*	−0.21 (0.06)*	−0.31 (0.08)*	0.34
Chance of liver damage developing	−0.10 (0.03)*	−0.42 (0.05)*	−0.23 (0.04)*	<0.01†
Chance of skin rash developing	−0.02 (0.02)	−0.05 (0.02)*	−0.05 (0.03)	0.53
Chance of fatigue developing	0.05 (0.02)*	−0.03 (0.02)	−0.03 (0.03)	0.69

SE, standard error; TB, tuberculosis.
* Significant preference within the class ($P < 0.05$).
† Significant difference across the three classes.

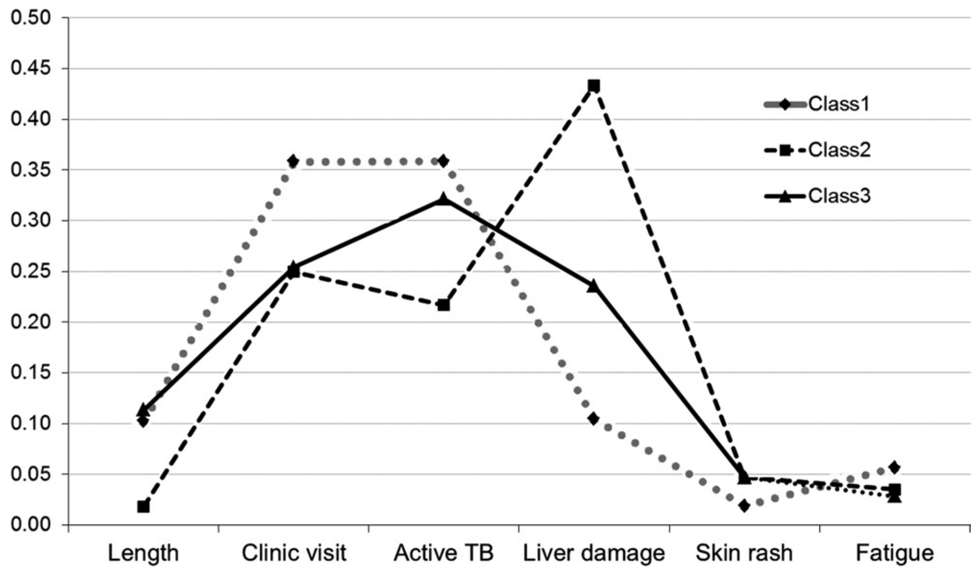

Fig. 3 – Relative importance of attributes.

and frequency of clinic visits (Fig. 3) in treatment choices. They preferred no clinic visits.

We found five sociodemographic factors that were significantly associated with the membership of preference classes, including origin of birth, having children, education level, employment status, and over-the-counter (OTC) medications. Table 4 describes the different sociodemographic profiles of the three classes. Individuals in class 1 were most likely to have children among the three classes (62.6% vs. 43.5% and 48.6%). Those in class 2 had the highest employment rate among respondents (78.3% vs. 66.1% and 41.8%). Class 3 respondents were most likely to be born outside Canada (97.7% vs. 80.0% and 85.9%), have higher education (college or higher: 95.0% vs. 78.5% and 74.8%), be unemployed (58.2% vs. 33.9% and 21.7%), and take OTC medications (27.4% vs. 14.7% and 12.1%).

Discussion

To our knowledge, this is the first study to quantify patient preferences for LTBI treatment using a DCE technique with a robust latent class analysis approach. Methodologically, our study illustrates how the DCE technique could be an internally consistent and valid tool to understand patient preferences for health products and interventions. The use of latent class analysis allows us to identify and categorize the preference heterogeneity among respondents. Incorporating sociodemographic variables could provide intuitive and informative information that could potentially help inform health-care practice.

As expected, respondents were consistently in favor of shorter length of treatment, lower risk of side effects, and higher effectiveness. Among the three side effects, respondents were much more concerned about the rare but serious one (i.e., liver damage) than the more common mild/moderate ones (i.e., skin rash and fatigue). These findings were generally plausible and congruent with our hypotheses, which greatly supported the theoretical validity of our DCE survey.

Three factors, the risk of active TB developing, the chance of liver damage developing, and the frequency of clinic visits, were the most important determinants on treatment decision making for the majority of respondents. Although previous studies found that the length of regimen was a critical predictor of LTBI treatment adherence and completion among patients receiving treatment [10–12], our results revealed that treatment benefits and potential side effects were more important than its length when patients decided whether to initiate the treatment. As we observed in practice, a fair proportion of patients agree to start the 9-month INH regimen but stop it after awhile, even without experiencing side effects. This suggests that initial decision making and treatment adherence are different behaviors and need to be examined and targeted differently.

Our results revealed that patients' preferences varied significantly when making decisions regarding LTBI preventive treatment. A three-latent-class model appeared to best fit our data. We associated the class membership with five measurable sociodemographic factors. Overall, the class-specific preferences made sense with the characteristics of each class.

Class 1 individuals may be representative of people who tend to adhere to the preventive treatment and the current practice at TB clinics (i.e., monthly clinic visits). They seemed to care a lot about getting rid of the infection and not be discouraged by the risk of a serious side effect (i.e., liver damage). They were most likely to have children. As we learned from patient interviews, an important motivating factor for many people to initiate the preventive treatment was to protect their family, especially children. Class 1 was the largest group, with approximately 47% of the sample, followed by class 2 with 32% and class 3 with 21%. In our sample of LTBI patients, however, people who refused or tended to refuse the preventive treatment might be underrepresented for two reasons. First, among people diagnosed with LTBI, a large proportion of them did not come to the TB clinic to discuss the preventive treatment. It was likely that these individuals had already made up their minds to refuse the treatment and did not bother to discuss it with a TB physician. Second, we observed that patients who eventually refused the treatment were less likely to agree to participate in our study. We were unable to investigate the differences between patients who agreed to participate and those who refused to participate due to ethics constraints.

Class 2 respondents were concerned most about the potential risk of liver damage. Those in class 2 had the highest employment rate and preferred less frequent clinic visits. One possible motivator for them to initiate the preventive treatment might be the obligation or pressure from school or work, mostly in health care or early education. Class 3 respondents had the highest probability of choosing the neither option in the DCE and might be likely to refuse the preventive treatment in reality. They were more likely to be born outside Canada, unemployed, highly educated, or taking OTC medications. Most of our respondents were born in Asian countries where BCG vaccination is a routine practice. The fact that the TST, the LTBI diagnostic test, is highly confounded by BCG may play a role in the high rate of those refusing the preventive treatment among the foreign born. For unemployed individuals, current living needs or being busy with school possibly left them little time or energy to consider preventing a disease that might only happen in the future. It is interesting that higher education was found to be associated with a tendency to refuse preventive treatment. It is possible that people with higher education tend to choose a healthy lifestyle and believe they have more control over their own health. They would be less concerned about an infectious disease such as TB, which is often associated with lower socioeconomic status.

There has been research attempting to identify factors that may affect or predict individual judgment of their preferences, e.g., sociodemographic features, individuals' risk attitudes (risk seeking vs. risk averse), and individuals' perceived control over their own health. In our study, we found a number of patients' sociodemographic factors were significantly associated with the preference heterogeneity that we observed. Previous studies yielded few results on this topic. One study showed that osteoarthritis patients' preferences varied widely in therapeutic decisions, but their clinical, sociodemographic, and psychological characteristics were not found to explain the heterogeneity [23]. This study, however, applied a probabilistic threshold technique, different from our DCE methodology.

Our results underline the importance and value of accounting for preference heterogeneity when analyzing choice data. Model-fit statistics suggested that latent class model fit our data better than traditional conditional logit model, and including sociodemographic covariates further improved the model fit. Latent class analysis provides richer information that would not be observed with more traditional conditional logit approaches. The use of latent class analysis allows us to categorize respondents' preferences and helps us better understand how respondents perceive the risks and benefits differently and weigh treatment attributes differently in decision making. This information could possibly assist health-care professionals in effective communication with patients when advocating preventive treatment, which would lead to improved treatment acceptance.

Methodological concerns over DCE's experimental design, sample size and selection, and choice data collection and analysis have been widely discussed. Although no definitive answers to the optimal sample size, a few issues are recommended to consider, e.g., the number of attributes, complexity of choice tasks, statistical approach used to analyze choice data, degree of desired precision, and budget [14,24]. In addition, an often-used rule in regression analysis suggests that a minimum of 10 dependent variable observations is required for each independent variable. Our sample size of 194 was enough to fit a latent class model with six attribute variables and five covariates.

We ensured the validity of the DCE design through carefully choosing treatment attributes by patient interviews and expert opinions and piloting the survey before final administration. To further improve the validity and quality of DCE choice data, a warm-up choice task was practiced with the researcher by each respondent before completing the survey. We also incorporated two fixed consistency-check questions in each version of the survey. Only 4.7% of the respondents failed both questions. These respondents were likely to not fully understand the DCE tasks and might not have made meaningful choices. Therefore, their responses were excluded from analysis to ensure the quality of our choice data. Further considering the fact that most respondents spoke English as their second language, our DCE survey was well understood and accepted. Finally, our results were clinically and practically plausible, which supported the theoretical validity of our DCE methodology.

The most expressed concern regarding the DCE technique has been that stated preference may not reflect true preference and not be able to predict individuals' real-life behavior in an actual market situation (i.e., revealed preference) [25–27]. In a well-controlled experimental context, DCE choice tasks may simplify real-life decision making, and respondents may be not willing or not able to express their true preferences. One effective approach to addressing this concern would be to compare the stated choices from the DCE survey with actual decision-making behavior, which would provide the strongest evidence to support the validity of the DCE technique. This is an important avenue for future research in applying DCE techniques in health care.

Conclusions

The DCE technique offers a promising tool to understand patients' decision-making processes regarding health products and services and to potentially inform health-care practice. To extend the usefulness of DCE in informing health-care practice, future effort should be directed to validating this technique. This study also highlights the use of latent class analysis in preference studies as an area of potentially novel research in health economics that requires further empirical applications.

Acknowledgments

We thank Dr. Larry Lynd for his valuable input during the survey design and result interpretation. We thank all physicians and nurses at the BCCDC TB clinics for their generous help in patient recruitment. We are also grateful to all respondents who participated in this research.

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